3. [Amended] The factor of claim 1 [lacking substantial] having less than about 2-3% binding reactivity with the antibody raised to plant-derived ouabain or mammalian ouabain-like sodium pump inhibitory factor (OLF).

4. [cancel] The factor of claim 1 having 10-fold lower potency than OLF and 3-fold higher potency than dho for inhibiting sodium pump activity.

REMARKS

Applicant has carefully reviewed and considered the Office Action mailed on October 1, 2002, and the documents cited therewith.

Claims 1-3 are amended, claim 4 is canceled, and claims 10-34 are withdrawn from consideration; as a result, claims 1-3, and 5-34 are now pending in this application, with claims 1-3, and 5-9 under examination at this time. No new subject matter has been added. The amendments are made to clarify the claims, and not for reasons relating to patentability. Therefore, the amendments are not intended to limit the scope of equivalents to which any claim element may be entitled.

Support for the amendments to claims is found throughout the specification. For example, support for the amendments to claim 1 can be found in originally filed claim 4, and at page 7, line 4 (definition of "dho").

Support for the amendment to claim 2 is found, for example, at page 26, lines 10-12 (Dh-OLF showed an identical chromatographic retention time to the standard dihydroouabain component dho-B).

Support for the amendment to claim 3 is found, for example, at page 27, lines 10-18 (ouabain antibodies showed 2-3% cross-reactivity with dihydroouabain or Dh-OLF).

Affirmation of Election

Restriction to one of the following claims was required: Group I (claims 1-9), Group II (claims 10-20), Group III (claims 21-23), Group IV (claims 24-26), Group V (claims 27-28), Group VI (claims 30-31) and Group VII (claims 32-22).

As provisionally elected by telephone by Applicant's representative, Ann Viksnins, on September 23, 2002, Applicant elects to prosecute the invention of Group I, claims 1-9. Applicant reserves the right to later file continuations or divisions having claims directed to the non-elected inventions.

Claim Objections

The examiner objected to claims 2 and 4 because of a formality. Namely, claims 2 and 4 refer to the abbreviation "dho" without the full name of the compound being first listed. This informality has now been corrected by amendment to the claim 2, and claim 4 has been cancelled.

§112 Rejection of the Claims

Claims 1-9 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the examiner indicates that the term "dihydroouabain-like factor" is indefinite, because the ordinary artisan would not know the metes and bounds of this term.

It should be noted that the term "dihydroouabain-like factor" (or "Dh-OLF") is a term well-known in the art as a distinct compound. There are four related compounds of interest in this application: ouabain, dihydroouabain (dho), ouabain-like factor (OLF), and dihydroouabain-like factor (Dh-OLF). "Ouabain" is a plant-derived cardiac glycoside that inhibits the catalytic activity of Na^+, K^+-ATPase. Qazzaz et al., *Bichim et Biophys. Acta* 1472 (1999) 486-497 (see Introduction). "Dihydroouabain" is synthetically made from this plant-derived ouabain, and is commonly used as a sodium pump antagonist. *Id.* Further, it is now known that the compound commonly known as "dho" comprises two different biologically active isomers, dho-A and dho-B. *Id.*

"OLF" is a mammalian cardenolide that is a counterpart to plant-derived ouabain. Qazzaz et al., *Endocrinology* 141 (2000) 3200-3209 (see Introduction). "Dh-OLF" is a distinct mammalian lactone-hydrogenated ouabain-like factor found, for example, in the secretions of cultured mouse adrenal Y-J cells. *Id.* In many ways Dh-OLF structurally and functionally

mimics plant-derived dho. *Id.* It is, however, structurally and functionally a distinct compound from ouabain, OLF, or dho. As used in the present application, the term "dihydroouabain-like factor" does not mean any generic compound that may be similar to dho, but a specific compound as this term is used in the published literature.

The examiner also stated that the terms "similar to" and "substantial" are indefinite. These terms have been deleted from the claims, thereby rendering this rejection moot.

Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

§102 Rejection of the Claims

Claims 1-9 were rejected under 35 U.S.C. § 102(b) as being anticipated by Repenning (U.S. 3,113,128).

Repenning discloses a chemical process for generating dihydroouabain (dho) from the plant-derived starting material ouabain. As discussed above, however, there is a structural and functional distinction between dho and the Dh-OLF recited by the present claims. The process to generate dho from ouabain described by Repenning actually generates both the dho-A and dho-B isomers of dho.

The present invention is to Dh-OLF. Dho and Dh-OLF can be distinguished by their sodium pump inhibition activity. The claimed Dh-OLF has a 3-fold higher potency than dho for inhibiting sodium pump activity. The claimed Dh-OLF also has a 10-fold lower potency than ouabain-like factor (OLF) for inhibiting sodium pump activity. Thus, Dh-OLF is clearly a patentably distinct compound from dho, OLF or ouabain.

Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 102(b) be withdrawn.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 C.F.R. § 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this ____ day of January, 2003.

Name _____ Signature _____

CLEAN VERSION OF PENDING CLAIMS

DIHYDROOUABAIN-LIKE FACTOR AND DIAGNOSTIC & THERAPEUTIC COMPOSITIONS AND METHODS
Applicant: Roland Valdes, Jr. et al.
Serial No.: 09/503,559

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1. [Amended] A purified mammalian dihydroouabain-like factor (Dh-OLF) having binding reactivity with antibody raised against plant-related dihydroouabain (dho), and having 10-fold lower potency than ouabain-like factor (OLF) for inhibiting sodium pump activity and 3-fold higher potency than dho for inhibiting sodium pump activity.

2. [Amended] The factor of claim 1 having the same high pressure liquid chromatography elution pattern as dho-B.

3. [Amended] The factor of claim 1 having less than about 2-3% binding reactivity with the antibody raised to plant-derived ouabain or mammalian ouabain-like sodium pump inhibitory factor (OLF).

4. [cancelled] The factor of claim 1 having 10-fold lower potency than OLF and 3-fold higher potency than dho for inhibiting sodium pump activity.

5. The factor of claim 1 which is of human origin.

6. The factor of claim 1 which is of bovine origin.

7. The factor of claim 1 which is obtained by reduction of OLF.

8. A pharmaceutical composition comprising the mammalian Dh-OLF factor of claim 1 and a pharmaceutically or veterinarily acceptable carrier.

9. The composition of claim 8 in the form of a formulation selected from the group consisting of oral, parenteral, ophthalmic, slow release and enteric coating formulations.

10. A method of prophylactically or therapeutically treating a condition associated with higher than normal sodium pump activity, comprising administering to a subject in need of the treatment an effective amount of the composition of claim 8.

11. The method of claim 10 wherein the composition is administered parenterally.

12. The method of claim 10 wherein the composition is administered orally.

13. The method of claim 10 wherein the composition is administered in an amount of about 1 *g/kg to about 1.5 mg/kg body weight.

14. The method of claim 11 wherein the subject is human.

15. The method of claim 11 wherein the disease or condition is heart disease, and the composition is administered in an effective amount.

16. The method of claim 16 wherein the heart disease is congestive heart failure.

17. The method of claim 11 where in the disease or condition is hypertension, and the composition is administered in an effective amount.

18. The method of claim 17 wherein the hypertension is selected from the group consisting of essential hypertension, thyroidism-induced hypertension, and pregnancy-induced or pregnancy-associated hypertension.

19. The method of claim 10 wherein the disease or condition is cataracts, and the composition is administered in an effective amount.

20. The method of claim 10 wherein the disease or condition is Alzheimer's disease, and the composition is administered in an effective amount.

21. A binding agent having affinity for the factor of claim 1.

22. The binding agent of claim 21 selected from the group consisting of polyclonal antibodies, monoclonal antibodies, F_V fragments and aptomers.

23. A pharmaceutic composition comprising the binding agent of claim 22 and a pharmaceutically or veterinarily acceptable carrier.

24. A method of prophylactically or therapeutically treating a condition associated with higher than normal OLF or DhOLF levels comprising administering to a subject in need of the treatment an effective amount of the composition of claim 23.

25. The method of claim 24, wherein the antibody is administered in an amount of about 0.1 to about 1000 *mol/kg body weight.

26. The method of claim 24 wherein the subject is human.

27. A quantitative method of detecting Dh-OLF in an animal sample, comprising
obtaining a test sample suspected of comprising Dh-OLF analyte;
contacting the test sample with a solid substrate-bound first binding agent having specificity for Dh-OLF or for dho isomer mixture but not for OLF, under conditions effective for said first binding agent to bind any analyte present in the sample and form binding agent-analyte complex(es);
contacting the substrate-bound first binding agent-analyte complex(es) with a labeled second binding agent specific to the first binding agent, under conditions effective to bind to any substrate-bound analyte-first agent to form a solid substrate-bound analyte-anti-Dh-OLF binding

agent- second-binding agent or analyte-anti-dho binding agent-second binding agent labeled complex(es);

detecting the amount of solid substrate-bound label; and

comparing that amount of complex(es) to the amount of complex(es) obtained for a known amount of a standard Dh-OLF or dho under the same or similar conditions.

28. The method of claim 26 wherein the binding agent comprises anti-Dh-OLF, anti-dho antibody, fragments or aptomers.

29. The method of claim 26 wherein the subject is human.

30. A quantitative method of detecting Dh-OLF in an animal sample comprising isolating Dh-OLF by HPLC and comparing the height of the peak characteristic of Dh-OLF to that of a known amount of dho-B separated in the same or similar manner.

31. The method of claim 30 wherein the sample is taken from a human.

32. A purified plant-related dho isomer.

33. The isomer of claim 32 that is dho-A.

34. The isomer of claim 32 that is dho-B.